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# Long-term Risks of Cirrhosis and Hepatocellular Carcinoma Across Steatotic Liver Disease Subtypes

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INTRODUCTION: **The prospective study aimed to investigate the long-term associated risks of cirrhosis and hepatocellular carcinoma (HCC) across various subtypes of steatotic liver disease (SLD).**

METHODS: **We enrolled 332,175 adults who participated in a health screening program between 1997 and 2013. Participants were categorized into various subtypes, including metabolic dysfunction-associated SLD (MASLD), MASLD with excessive alcohol consumption (MetALD), and alcohol-related liver disease (ALD), based on ultrasonography findings, alcohol consumption patterns, and cardiometabolic risk factors. We used computerized data linkage with nationwide registries from 1997 to 2019 to ascertain the incidence of cirrhosis and HCC.**

RESULTS: **After a median follow-up of 16 years, 4,458 cases of cirrhosis and 1,392 cases of HCC occurred in the entire cohort, resulting in an incidence rate of 86.1 and 26.8 per 100,000 person-years, respectively. The ALD group exhibited the highest incidence rate for cirrhosis and HCC, followed by MetALD, MASLD, and non-SLD groups. The multivariate adjusted hazard ratios for HCC were 1.92 (95% confidence interval [CI] 1.51–2.44), 2.91 (95% CI 2.11–4.03), and 2.59 (95% CI 1.93–3.48) for MASLD, MetALD, and ALD, respectively, when compared with non-SLD without cardiometabolic risk factors. The pattern of the associated risk of cirrhosis was similar to that of HCC (all *P* value <0.001). The associated risk of cirrhosis for ALD increased to 4.74 (95% CI 4.08–5.52) when using non-SLD without cardiometabolic risk factors as a reference.**

DISCUSSION: **This study highlights elevated risks of cirrhosis and HCC across various subtypes of SLD compared with non-SLD, emphasizing the importance of behavioral modifications for early prevention.**

**KEYWORDS:** end-stage liver disease; long-term risk; fatty liver disease; cardiometabolic factor; alcohol

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## INTRODUCTION

Global urbanization, coupled with changes in dietary habits and lifestyles, has led to a steady rise in obesity rates worldwide. High-risk behaviors, such as alcohol consumption and central adiposity, play significant roles in driving chronic liver disease and mortality after diagnosis (1). This surge in obesity is closely associated with a growing spectrum of chronic diseases. High body mass index (BMI) has been linked to as much as 17% of liver cancer cases, presenting a substantial public health burden (2).

It is well established that overweight and obesity are strongly associated with steatotic liver disease (SLD), previously termed nonalcoholic fatty liver disease (NAFLD), one of the major contributors to hepatocellular carcinoma (HCC) (3). To address the limitations of the previous NAFLD definition, which excluded individuals with excessive alcohol consumption and other

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underlying liver conditions, a new term, metabolic dysfunction-associated fatty liver disease (MAFLD) (4), was introduced. This aimed to offer a more precise representation of the underlying metabolic processes and the diverse nature of the disease. However, MAFLD encompassed individuals with fatty liver regardless of alcohol consumption and required at least 2 metabolic risk factors for classification, potentially leading to the misclassification of patients with varying underlying causes (5). Moreover, the continued use of the term "fatty" was considered stigmatizing. Consequently, the term metabolic dysfunction-associated SLD (MASLD) was proposed to redefine individuals with SLD and categorize patients into distinct subtypes (6).

The new definition stratified individuals with SLD into 4 major groups. Those with limited alcohol consumption and at least 1 cardiometabolic risk factor were classified as MASLD. A subgroup, termed MetALD, was introduced for individuals with both MASLD and increased alcohol intake, recognizing the coexistence of metabolic and alcohol-related risk factors. Furthermore, alcoholic liver disease (ALD) was delineated as a distinct group where steatosis was one of the features. ALD highlights alcohol as a driving factor in liver pathogenesis and underscores the impact of excessive alcohol consumption (7).

The objective of this prospective study was to assess the incidence of cirrhosis and HCC among various SLD subtypes. We estimated the associated risks of cirrhosis and HCC across different SLD subtypes by comparing with non-SLD or non-SLD without cardiometabolic risk factors.

## METHODS

### Study population and data collection

The study participants consisted of 421,941 adults aged 30 years and older who participated in a health screening program managed by a private healthcare institution in Taiwan between 1997 and 2013. Upon enrollment, all participants underwent a series of blood, urine, and anthropometric tests as well as physical examinations. They also completed a structured questionnaire on sociodemographic characteristics, lifestyle, and personal and family medical histories. Virological and biochemical tests, including hepatitis B surface antigen (HBsAg) or antibodies against hepatitis C virus (anti-HCV), platelet counts, alfa-fetoprotein, aspartate aminotransferase, and alanine aminotransferase, were performed on blood samples. Each participant provided signed informed consent regarding the use of data generated from medical screenings for biomedical investigations. Detailed information on the study population has been described (8). The study protocol was approved by the Institutional Review Board of National Yang Ming Chiao Tung University, Taipei, Taiwan.

### Definition of MASLD, cryptogenic SLD, MetALD, and ALD

All study participants underwent high-resolution real-time abdominal ultrasonography performed by board-certified gastroenterologists, to detect the presence or absence of steatosis. We excluded participants with a prevalence of either cirrhosis or HCC, those who were seropositive for HBsAg or anti-HCV, and those lacking adequate data on alcohol intake or ultrasonography, resulting in 332,175 participants in a target study population (Figure 1). Among them, 129,802 (39.1%) exhibited SLD as detected by ultrasonography. We further categorized them into various subtypes, including MASLD, cryptogenic SLD, MetALD, and ALD, based on their cardiometabolic risk factors and alcohol intake levels. Limited alcohol intake was defined as $<$10 g/d for women and $<$20 g/d for men following the Asian-Pacific Guideline (9). Excessive alcohol intake was defined as the amount of $>$40 g/d for women and $>$50 g/d for men. Moderate alcohol intake fell between these definitions, defined as 10–40 g/d for women and 20–50 g/d for men. According to consensus guidelines (6), individuals with limited alcohol intake and at least 1 cardiometabolic risk factor were classified as MASLD while those without any cardiometabolic risk factors were labeled as cryptogenic SLD. Participants with moderate alcohol consumption and at least 1 cardiometabolic risk factor were categorized as MetALD. Finally, individuals with moderate alcohol intake but lacking cardiometabolic risk factors and those with excessive alcohol consumption were designated as ALD.

### Follow-up and ascertainment of incident cirrhosis and HCC

To ascertain the incidence of end-stage liver diseases (cirrhosis and HCC) and vital status from January 1, 1997, to December 31, 2019, we used computerized data linkage using 3 nationwide registries: the National Health Insurance database, the National Cancer Registration Profiles, and the National Death Certification system, which cover nearly 100% of the Taiwanese population. These comprehensive registries, established by the Ministry of Health and Welfare in Taiwan, provide complete and accurate administrative and claims data, making them ideal for biomedical research (10). For cirrhosis diagnosis, we used the National Health Insurance database, identifying patients meeting at least 1 hospital admission code or with 2 or more outpatient visits. The date of first hospital admission or outpatient visit served as incident event date. We used the *International Classification of Disease, Ninth Revision* (*ICD-9*) codes 571.2 and 571.5 and *ICD-10* codes K70.2, K70.3, and K74 to identify cirrhosis events (11,12). To detect HCC occurrence and diagnostic dates, we conducted computerized data linkage with the National Cancer Registry, identifying HCC using *ICD-9* codes 155.0 and 155.2 and *ICD-10* code C22 (but excluded C22.1).

### Statistical methods

We calculated the person-years of follow-up for each participant starting from the study entry date until the date of cirrhosis or HCC diagnosis, death, or the last computerized data linkage with the national health profiles (i.e., December 31, 2019), whichever came first. To determine incidence rates of cirrhosis and HCC, we divided the number of newly diagnosed cases by person-years of follow-up. The cumulative risks of cirrhosis and HCC for population with various SLD subtypes were estimated using the Kaplan-Meier method, and differences in statistical significance were examined using log-rank tests. Crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for MASLD, MetALD, and ALD were obtained using Cox proportional hazards models. The proportionality assumptions (nonchanging HRs over time) of Cox models were examined, and no violation was detected. Potential confounders considered including age, sex, cigarette smoking, alpha-fetoprotein levels, and Fibrosis-4 Index (calculated using a formula involving age, aspartate aminotransferase, alanine aminotransferase, and platelet counts). We calculated incidence rates of cirrhosis and HCC by various subtypes of SLD. However, we did not estimate the cumulative risks or HRs (95% CI) for cryptogenic SLD due to the limited number of cirrhosis and HCC cases in this group. In addition, we conducted sensitivity analyses, using non-SLD individuals without any cardiometabolic risk factors as a reference group, to examine

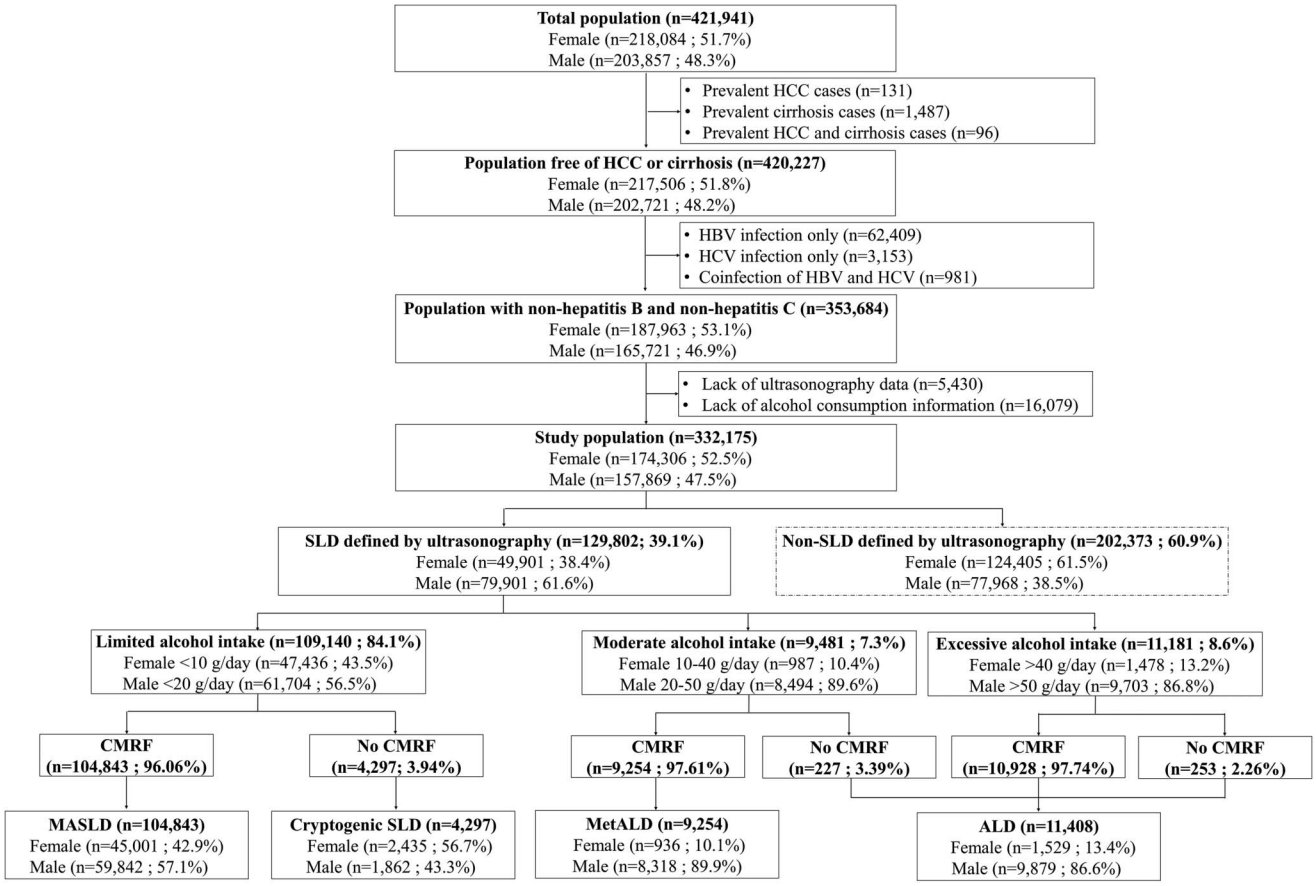



**Figure 1.** Flowchart of the study population and definition of SLD subtypes. ALD, alcohol-associated liver disease; CMRF, cardiometabolic risk factor; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD and increased alcohol intake; SLD, steatotic liver disease.

the associated risks of cirrhosis and HCC among various SLD subtypes. Statistical significance was defined as a 2-sided *P* value of $<0.05$. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

## RESULTS

### Baseline characteristics and study population

Table 1 summarizes the baseline characteristics of the study population. Among the 129,802 participants with SLD, 109,140 (84.1%) had limited alcohol intake. In each category of alcohol intake, approximately 96%–97% had at least 1 cardiometabolic risk factor. Furthermore, 104,843 (80.8%) were categorized as MASLD, 4,297 (3.3%) as cryptogenic SLD, 9,254 (7.1%) as MetALD, and 11,408 (8.8%) as ALD. At baseline, individuals in the MASLD, MetALD, and ALD groups tended to be older, have obesity (BMI $\geq$25 kg/m$^2$ or central obesity), and were more likely to have metabolic syndrome compared with the non-SLD and cryptogenic SLD groups. Moreover, MetALD and ALD had higher proportions of men and cigarette smokers.

### Incidence of cirrhosis and HCC in various SLD subtypes

After a total of 5,179,485.3 person-years of follow-up, 4,458 cases of cirrhosis occurred in the entire cohort, resulting in an incidence rate of 86.1 per 100,000 person-years. The ALD group exhibited the highest incidence of cirrhosis, with a rate of 282.0 per 100,000 person-years, followed by the MetALD and MASLD groups, which had rates of 145.6 and 95.4 per 100,000 person-years, respectively. All of these subgroups had elevated cirrhosis incidence compared with the non-SLD group (69.3 per 100,000 person-years). Among the non-SLD group, 36.4% had no cardiometabolic risk factors, resulting in the lowest incidence rate of 32.3 per 100,000 person-years (Table 2). Figure 2a illustrates the cumulative risk of cirrhosis during follow-up, showing significant differences: 6.9% for ALD, 3.2% for MetALD, 3.1% for MASLD, and 2.0% for non-SLD (*P*-value $<0.0001$).

The pattern of HCC incidence paralleled that of cirrhosis. After 5,203,878.9 person-years of follow-up, 1,392 newly diagnosed HCC cases occurred, with an incidence rate of 26.8 per 100,000 person-years. The incidence rates of the 5 groups, in a descending order, were ALD, MetALD, MASLD, non-SLD, and non-SLD without any cardiometabolic risk factors, with rates of 69.0, 52.7, 30.7, 21.8, and 7.8 per 100,000 person-years, respectively. Approximately 1.8% of ALD and 1.6% of MetALD developed HCC during follow-up. The cumulative risk of HCC in MASLD was half that of ALD. There were significant differences in the cumulative risk of HCC among the various subtypes (*P*-value $<0.0001$).

### Relative risks of cirrhosis and HCC by SLD subtypes

Table 3 shows the relative risks of cirrhosis and HCC associated with different SLD subtypes compared with non-SLD. The adjusted HR (95% CI) for HCC was 1.31 (1.16–1.47), 1.83 (1.43–2.34), and 1.52 (1.24–1.86) for MASLD, MetALD, and

**Table 1.** Baseline characteristics of study population (N = 332,175)

| Baseline characteristics | Total (N = 332,175) n (%) | Non-SLD (n = 202,373) n (%) | MASLD (n = 104,843) n (%) | Cryptogenic SLD (n = 4,297) n (%) | MetALD (n = 9,254) n (%) | ALD (n = 11,408) n (%) |
|---|---|---|---|---|---|---|
| Age (yr) | | | | | | |
| Mean ± SD | 44.07 ± 12.31 | 42.35 ± 11.95 | 47.03 ± 12.54 | 40.08 ± 9.23 | 45.70 ± 11.68 | 47.48 ± 11.63 |
| 30–<40 | 156,529 (47.1) | 109,325 (54.0) | 37,802 (36.1) | 2,510 (58.4) | 3,436 (37.1) | 3,456 (30.3) |
| 40–<50 | 73,051 (22.0) | 42,307 (20.9) | 23,836 (22.7) | 1,069 (24.9) | 2,580 (27.9) | 3,259 (28.6) |
| 50–<60 | 55,919 (16.8) | 27,461 (13.6) | 23,280 (22.2) | 521 (12.1) | 1,916 (20.7) | 2,741 (24.0) |
| 60–<70 | 34,257 (10.3) | 16,492 (8.2) | 15,064 (14.4) | 176 (4.1) | 1,001 (10.8) | 1,524 (13.4) |
| ≧70 | 12,419 (3.7) | 6,788 (3.4) | 4,861 (4.6) | 21 (0.5) | 321 (3.5) | 428 (3.8) |
| Sex | | | | | | |
| Female | 174,306 (52.5) | 124,405 (61.5) | 45,001 (42.9) | 2,435 (56.7) | 936 (10.1) | 1,529 (13.4) |
| Male | 157,869 (47.5) | 77,968 (38.5) | 59,842 (57.1) | 1,862 (43.3) | 8,318 (89.9) | 9,879 (86.6) |
| BMI (kg/m$^2$) | | | | | | |
| Mean ± SD | 23.38 ± 3.56 | 21.75 ± 2.68 | 26.08 ± 3.21 | 21.45 ± 1.21 | 26.13 ± 3.02 | 25.99 ± 3.28 |
| <18.5 | 21,050 (6.3) | 20,732 (10.3) | 139 (0.1) | 106 (2.5) | 15 (0.2) | 58 (0.5) |
| 18.5–<23 | 141,558 (42.6) | 120,161 (59.4) | 14,292 (13.6) | 4,189 (97.5) | 1,085 (11.7) | 1,831 (16.1) |
| 23–<25 | 71,741 (21.6) | 38,556 (19.1) | 28,115 (26.8) | 0 (0.0) | 2,376 (25.7) | 2,694 (23.6) |
| ≥25 | 97,737 (29.4) | 22,874 (11.3) | 62,267 (59.4) | 0 (0.0) | 5,776 (62.4) | 6,820 (59.8) |
| Missing | 89 | | | | | |
| Central obesity[a] | | | | | | |
| No | 254,743 (77.9) | 182,654 (91.8) | 56,917 (55.0) | 4,250 (99.8) | 5,038 (55.2) | 5,884 (52.5) |
| Yes | 72,285 (22.1) | 16,237 (8.2) | 46,626 (45.0) | 10 (0.2) | 4,088 (44.8) | 5,324 (47.5) |
| Missing | 5,147 | | | | | |
| Metabolic syndrome[b] | | | | | | |
| No | 258,391 (77.8) | 185,345 (91.6) | 58,378 (55.7) | 4,297 (100.0) | 4,843 (52.3) | 5,528 (48.5) |
| Yes | 73,784 (22.2) | 17,028 (8.4) | 46,465 (44.3) | 0 (0.0) | 4,411 (47.7) | 5,880 (51.5) |
| Family history of liver cancer | | | | | | |
| No | 309,486 (93.2) | 188,392 (93.1) | 97,889 (93.4) | 3,947 (91.9) | 8,616 (93.1) | 10,642 (93.3) |
| Yes | 22,572 (6.8) | 13,874 (6.9) | 6,946 (6.6) | 350 (8.2) | 638 (6.9) | 764 (6.7) |
| Missing | 117 | | | | | |
| Smoking | | | | | | |
| Never | 218,249 (67.3) | 140,346 (71.1) | 69,452 (67.8) | 3,119 (74.1) | 2,492 (27.6) | 2,840 (25.7) |
| Ever | 105,852 (32.7) | 57,045 (28.9) | 32,984 (32.2) | 1,093 (26.0) | 6,535 (72.4) | 8,195 (74.3) |
| Missing | 8,074 | | | | | |
| ALT (IU/L) | | | | | | |
| Mean ± SD | 26.29 ± 24.21 | 20.05 ± 18.96 | 35.92 ± 27.51 | 23.54 ± 16.68 | 39.38 ± 28.46 | 39.23 ± 33.54 |
| <40 | 283,383 (85.4) | 191,208 (94.5) | 74,599 (71.3) | 3,864 (90.0) | 6,059 (65.9) | 7,653 (67.6) |
| ≥40 | 48,292 (14.6) | 11,068 (5.5) | 29,994 (28.7) | 430 (10.0) | 3,134 (34.1) | 3,666 (32.4) |
| Missing | 500 | | | | | |
| AST (IU/L) | | | | | | |
| Mean ± SD | 22.98 ± 14.13 | 20.82 ± 12.68 | 25.95 ± 13.58 | 21.11 ± 8.43 | 28.08 ± 16.42 | 30.53 ± 28.00 |
| <40 | 315,377 (95.1) | 197,734 (97.8) | 95,571 (91.4) | 4,197 (97.7) | 8,153 (88.7) | 9,722 (85.9) |
| ≥40 | 16,288 (4.9) | 4,541 (2.2) | 9,015 (8.6) | 97 (2.3) | 1,040 (11.3) | 1,595 (14.1) |
| Missing | 510 | | | | | |

**Table 1.** (*continued*)

| Baseline characteristics | Total (N = 332,175) n (%) | Non-SLD (n = 202,373) n (%) | MASLD (n = 104,843) n (%) | Cryptogenic SLD (n = 4,297) n (%) | MetALD (n = 9,254) n (%) | ALD (n = 11,408) n (%) |
|---|---|---|---|---|---|---|
| AFP (ng/mL) | | | | | | |
| Mean ± SD | 3.36 ± 78.46 | 3.41 ± 100.47 | 3.23 ± 4.24 | 3.02 ± 2.17 | 3.47 ± 4.06 | 3.64 ± 4.47 |
| <6 | 315,759 (95.3) | 192,729 (95.5) | 99,783 (95.4) | 4,098 (95.7) | 8,673 (93.8) | 10,476 (92.0) |
| ≥6 | 15,675 (4.7) | 9,152 (4.5) | 4,854 (4.6) | 183 (4.3) | 571 (6.2) | 915 (8.0) |
| Missing | 741 | | | | | |
| Platelet ($10^3/\mu L$) | | | | | | |
| Mean ± SD | 246.39 ± 57.01 | 243.24 ± 56.51 | 252.66 ± 57.79 | 253.24 ± 57.07 | 244.74 ± 53.63 | 243.43 ± 56.44 |
| <150 | 6,890 (2.1) | 4,617 (2.3) | 1,718 (1.6) | 47 (1.1) | 192 (2.1) | 316 (2.8) |
| 150–400 | 321,163 (96.7) | 195,436 (96.6) | 101,565 (96.9) | 4,187 (97.5) | 8,986 (97.1) | 10,989 (96.4) |
| >400 | 4,054 (1.2) | 2,277 (1.1) | 1,544 (1.5) | 59 (1.4) | 74 (0.8) | 100 (0.9) |
| Missing | 68 | | | | | |
| FIB-4[c] | | | | | | |
| Mean ± SD | 0.92 ± 0.58 | 0.92 ± 0.56 | 0.92 ± 0.57 | 0.77 ± 0.36 | 0.94 ± 0.61 | 1.06 ± 0.81 |
| <1.45 | 293,127 (88.4) | 179,485 (88.7) | 92,063 (88.0) | 4,085 (95.2) | 8,066 (87.7) | 9,428 (83.3) |
| 1.45-<3.25 | 36,649 (11.1) | 21,643 (10.7) | 12,042 (11.5) | 202 (4.7) | 1,060 (11.5) | 1,702 (15.0) |
| ≥3.25 | 1,868 (0.6) | 1,135 (0.6) | 475 (0.5) | 4 (0.1) | 67 (0.7) | 187 (1.7) |
| Missing | 531 | | | | | |

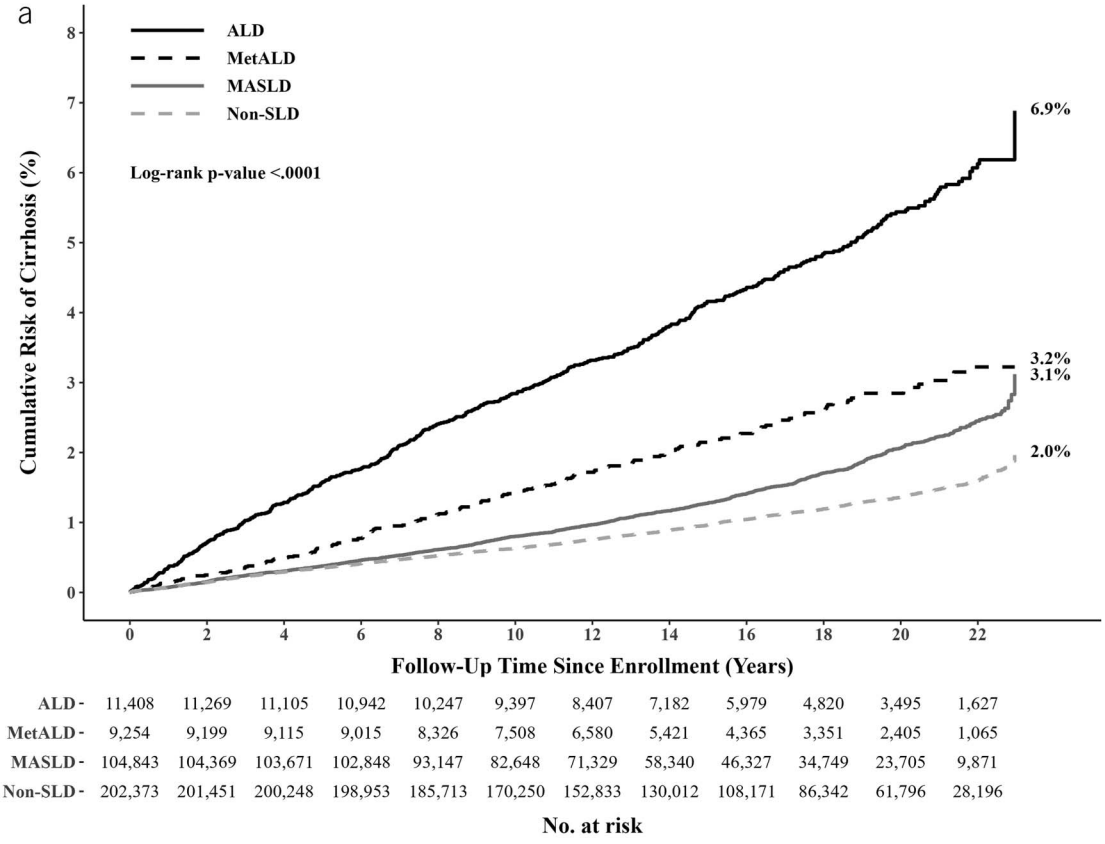
AFP, alpha-fetoprotein; ALD, alcohol-associated liver disease; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, Fibrosis-4 Index; HDL, high-density lipoprotein; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD and increased alcohol intake; SLD, steatotic liver disease.
[a]Central obesity: waist circumference ≥90 cm for men and ≥80 cm for women.
[b]Metabolic syndrome (meet 3 or more criteria listing below): (i) blood pressure ≥130/85 mm Hg or specific antihypertensive drug treatment, (ii) fasting glucose ≥100 or treatment of type 2 diabetes, (iii) plasma triglyceride ≥150 mg/dL or lipid-lowering treatment, (iv) plasma HDL-cholesterol ≤40 mg/dL for men and ≤50 mg/dL for women or lipid-lowering treatment, and (v) waist circumference ≥90 cm for men and ≥80 cm for women.
[c]FIB-4 formula: age (years) × AST (IU/L)/(platelets [$10^3/\mu L$] × ALT [IU/L]$^{1/2}$).

ALD, respectively, compared with non-SLD. The pattern for the associated risk of cirrhosis was similar, but ALD exhibited a higher cirrhosis risk, with an adjusted HR of 2.82 (2.54–3.13). In addition, when comparing these subtypes with non-SLD participants without any cardiometabolic risk factors, the associated risks of cirrhosis and HCC increased further. The adjusted HR for cirrhosis was 2.03 (1.79–2.29) for MASLD, 2.89 (2.40–3.48) for MetALD, and 4.74 (4.08–5.52) for ALD. Similarly, the associated risks for HCC were 1.92 (1.51–2.44) for MASLD, 2.91 (2.11–4.03) for MetALD, and 2.59 (1.93–3.48) for ALD.

**Table 2. Incidence rates of cirrhosis and HCC among different subtypes of SLD**

| | | Cirrhosis | | | HCC | | |
|---|---|---|---|---|---|---|---|
| SLD status | Total | Events | Person-years of follow-up | Incidence rates per 100,000 person-years (95% CI) | Events | Person-years of follow-up | Incidence rates per 100,000 person-years (95% CI) |
| Total population | 332,175 | 4,458 | 5,179,485.3 | 86.1 (83.6–88.6) | 1,392 | 5,203,878.9 | 26.8 (25.4–28.2) |
| Non-SLD | 202,373 | 2,243 | 3,238,723.0 | 69.3 (66.4–72.2) | 709 | 3,251,545.1 | 21.8 (20.2–23.5) |
| Without CMRF | 73,758 | 366 | 1,132,516.9 | 32.3 (29.1–35.8) | 88 | 1,134,642.9 | 7.8 (6.2–9.6) |
| SLD | | | | | | | |
| MASLD | 104,843 | 1,489 | 1,561,198.0 | 95.4 (90.6–100.4) | 481 | 1,568,923.6 | 30.7 (28.0–33.5) |
| Cryptogenic SLD | 4,297 | 13 | 58,250.6 | 22.3 (11.9–38.2) | 1 | 58,332.0 | 1.7 (0.0–9.5) |
| MetALD | 9,254 | 206 | 141,503.3 | 145.6 (126.4–166.9) | 75 | 142,434.8 | 52.7 (41.4–66.0) |
| ALD | 11,408 | 507 | 179,810.3 | 282.0 (258.0–307.6) | 126 | 182,643.4 | 69.0 (57.5–82.1) |

ALD, alcohol-associated liver disease; CI, confidence interval; CMRF, cardiometabolic risk factor; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD and increase alcohol intake; SLD, steatotic liver disease.



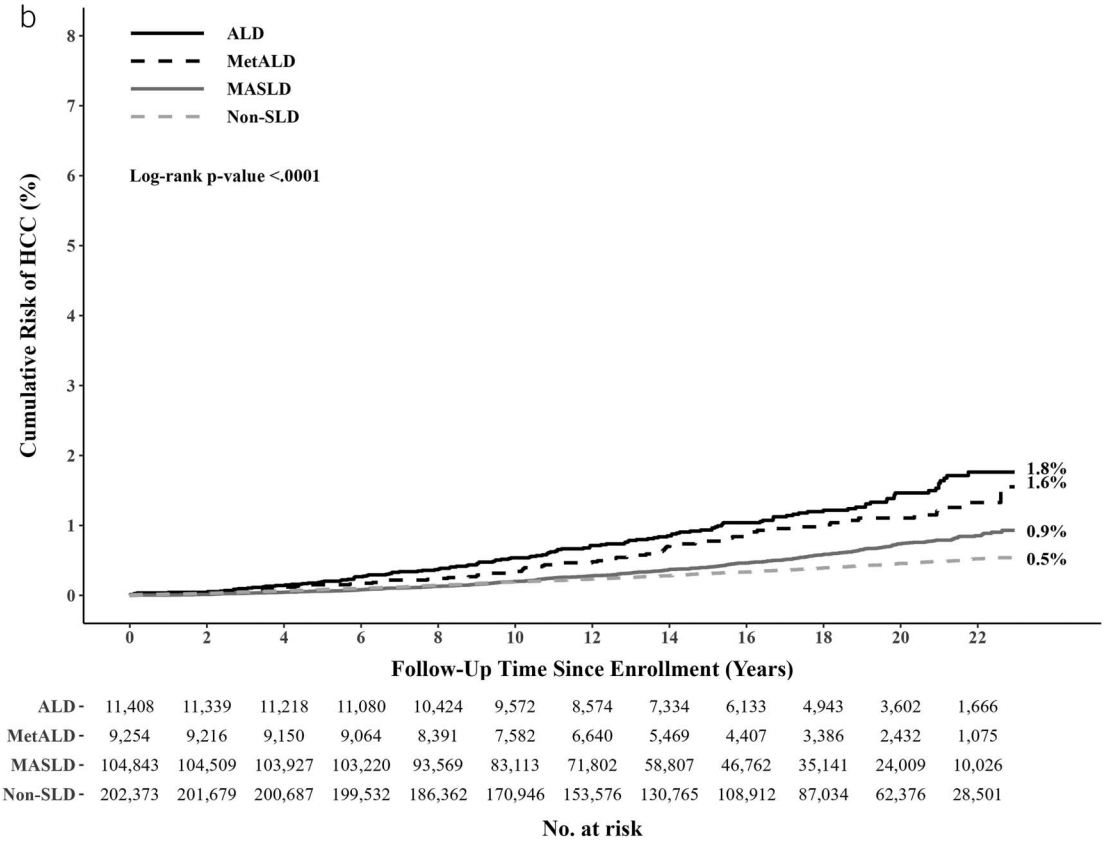




**Figure 2.** Cumulative risk of (**a**) cirrhosis and (**b**) HCC across SLD subtypes (n = 327,878). ALD, alcohol-associated liver disease; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD and increased alcohol intake; SLD, steatotic liver disease.

**Table 3. Relative risks of cirrhosis and HCC among SLD subtypes compared with non-SLD and non-SLD without CMRFs**

| | Model 1 <Non-SLD as a reference> | | | | Model 2 <Non-SLD without CMRF as a reference> | | | |
|---|---|---|---|---|---|---|---|---|
| Outcome | Crude HR (95% CI) | *P* value | Multivariate adjusted HR[a] (95% CI) | *P* value | Crude HR (95% CI) | *P* value | Multivariate adjusted HR[a] (95% CI) | *P* value |
| Cirrhosis | | | | | | | | |
| MASLD | 1.40 (1.31–1.50) | <0.0001 | 1.30 (1.21–1.39) | <0.0001 | 2.96 (2.64–3.32) | <0.0001 | 2.03 (1.79–2.29) | <0.0001 |
| MetALD | 2.12 (1.84–2.45) | <0.0001 | 1.72 (1.48–2.00) | <0.0001 | 4.47 (3.77–5.30) | <0.0001 | 2.89 (2.40–3.48) | <0.0001 |
| ALD | 4.07 (3.69–4.48) | <0.0001 | 2.82 (2.54–3.13) | <0.0001 | 8.52 (7.45–9.75) | <0.0001 | 4.74 (4.08–5.52) | <0.0001 |
| HCC | | | | | | | | |
| MASLD | 1.45 (1.29–1.63) | <0.0001 | 1.31 (1.16–1.47) | <0.0001 | 3.99 (3.18–5.00) | <0.0001 | 1.92 (1.51–2.44) | <0.0001 |
| MetALD | 2.46 (1.94–3.12) | <0.0001 | 1.83 (1.43–2.34) | <0.0001 | 6.72 (4.94–9.14) | <0.0001 | 2.91 (2.11–4.03) | <0.0001 |
| ALD | 3.16 (2.61–3.82) | <0.0001 | 1.52 (1.24–1.86) | <0.0001 | 8.55 (6.51–11.23) | <0.0001 | 2.59 (1.93–3.48) | <0.0001 |

ALD, alcohol-associated liver disease; CI, confidence interval; CMRF, cardiometabolic risk factor; HCC, hepatocellular carcinoma; HR, hazard ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD and increase alcohol intake; SLD, steatotic liver disease.
[a]Multivariate adjusted models: (i) cirrhosis adjusted for age, sex, smoking, and Fibrosis-4 Index. (ii) HCC adjusted for age, sex, smoking, alpha-fetoprotein, Fibrosis-4 Index, and family history of liver cancer.

We conducted a sensitivity analysis by excluding patients with Fibrosis-4 ≥3.25, reassessing the impacts of various steatotic subtypes on cirrhosis in comparison with non-SLD. The results remained consistent with our initial findings. The multivariate adjusted HR for cirrhosis was 1.99 (1.75–2.27) for MASLD, 2.90 (2.38–3.53) for MetALD, and 4.72 (4.01–5.55) for ALD in comparison with non-SLD without any cardiometabolic risk factors.

## DISCUSSION

Our prospective study comprehensively evaluated and compared the incidence of cirrhosis or HCC among various SLD subtypes, examining their long-term associated risks compared with those without SLD. This provides further insights into the natural history of SLD following the introduction of new definition.

The transition in nomenclature, from NAFLD to MAFLD and now to MASLD, reflects our ongoing commitment to improving disease awareness, reducing stigma, and enhancing liver disease diagnosis. The shift from NAFLD to MAFLD has prompted extensive research and scientific discussions (13–15). MAFLD criteria have proven practical in identifying patients with SLD showing significant hepatic fibrosis and a higher risk of disease progression (16). Moreover, MAFLD has been associated with significantly higher cardiovascular mortality compared with NAFLD (14). Concordance between NAFLD and MAFLD definitions was high, with 81%–93% of individuals with SLD fitting into either category (13). Clinical characteristics of those classified as NAFLD or MAFLD showed no significant differences (13). After the adoption of the new term, MASLD, 89.2% of individuals with intrahepatic triglyceride content >5% met the criteria for NAFLD, MAFLD, and MASLD, suggesting limited discrepancies between these definitions (17). In adddition, these different SLD definitions may have identical natural history of end-stage liver disease (18). However, MASLD's integration of previous concerns may categorize homogeneous groups with various liver disease etiologies, potentially leading to the development of future biomarkers or clinical trials.

Compared with MAFLD, MASLD provided a more comprehensive approach to addressing the impact of alcohol intake, a significant risk factor of cirrhosis and HCC (19,20). A substantial proportion of the Asian population carries genetic variants that affect the enzymes of alcohol dehydrogenase and aldehyde dehydrogenase, responsible for metabolizing alcohol into acetaldehyde and subsequently into acetate (21,22). Individuals with these variants experience the toxic and unpleasant effects of acetaldehyde, which often discourages alcohol consumption, leading to reduced alcohol intake (21). Consequently, we adjusted our criteria and used a relatively lower threshold to define excessive alcohol consumption (9). In our study population, women with moderate or heavy alcohol intake (≥10 g/d) accounted for 5% while men with similar alcohol consumption (≥20 g/d) represented 22%, indicating a predominance of increased alcohol consumption among men (23). Our findings suggested that, in addition to the associated risk of MASLD, both MetALD and ALD subgroups exhibited elevated risks of cirrhosis and HCC compared with non-SLD or those without cardiometabolic risk factors. This supports that excessive alcohol consumption and presence of metabolic syndrome are independent predictors of increased risks of mortality (24). Our findings are consistent with a previous study indicating patients with steatosis still face increased risks of advanced liver disease even with low alcohol intake (25). However, further investigation is required to determine the safe limits of alcohol consumption concerning the progression of cirrhosis or HCC.

Our study found that 39% of individuals exhibited SLD as detected by ultrasonography, consistent with recent findings reporting a 40% prevalence of steatosis by transient elastography (26). Among those diagnosed with SLD, 96% (125,025/129,802) had at least 1 cardiometabolic risk factor, suggesting that these factors serve as indicators for SLD. Conversely, the remaining 3.3% (4,297 of 129,802) of individuals with SLD lacking cardiometabolic risk factors were classified as having cryptogenic SLD. None of these individuals were overweight or obese (all had BMI <23 kg/m$^2$), and they exhibited relatively low incidences of cirrhosis and HCC. Furthermore, 63.6% (128,615 of 202,373) of individuals without SLD had at least 1 cardiometabolic risk factor. Therefore, we conducted additional analyses by comparing these different SLD subtypes with individuals without

SLD but with an absence of cardiometabolic risk factors. This analysis revealed an increased relative risk of cirrhosis and HCC for these SLD subtypes. The population's attributable fraction of metabolic factors (excess body weight and type 2 diabetes) for liver cancer was approximately 12%, and this fraction increased with age (27). This suggests that factors such as slower metabolism, reduced physical activity, and lower energy expenditure in adults of advanced age may contribute (28). These findings underscore the importance of behavioral modifications, including weight management, healthy dietary choices, and physical activity, in liver cancer prevention, regardless of the presence of SLD. This is particularly significant in an era characterized by an aging population.

Despite the increasing prevalence of SLD in recent decades, hepatitis B virus (HBV) and HCV infections remain significant contributors to cirrhosis and HCC in the Asian-Pacific region (29). In our study, we excluded individuals seropositive for HBsAg and anti-HCV to minimize potential confounding, thereby restricting to participants categorized as non-hepatitis B and non-hepatitis C. However, it is important to interpret these results cautiously as we cannot entirely rule out the possibility of past or current HBV infections. Before Taiwan's nationwide vaccination program was initiated in 1984, chronic HBV prevalence was as high as 20% (30). All of our study participants were born before the vaccination program. While we excluded individuals seropositive for HBsAg, some may have been exposed to HBV and could still be seropositive for anti-HB core antibodies, indicating past HBV infection. It has been previously reported that anti-HB core seroprevalence was approximately 80% among adults born before 1984 (31). Importantly, the presence of anti-HB core antibodies should not differ among various SLD subtypes and is unlikely to influence our findings.

Our study possesses several notable strengths. First, the study population underwent thorough health checkups, providing comprehensive information about multiple risk factors. Importantly, all study participants underwent abdominal ultrasonography, ensuring the accurate detection of hepatic steatosis. This approach enhances the reliability of our results and reinforces the validity of our conclusions. In addition, our study benefits from a large population sample, with an average follow-up period of approximately 15 years. This extended duration allowed for the accumulation of a substantial number of cirrhosis and HCC cases, establishing a robust foundation for comparing various subtypes of SLD. The study end points were defined through computerized data linkage with nationwide registries, ensuring complete follow-up of all participants and high-precision disease ascertainment. Although we identify patients with cirrhosis by using ICD codes in the National Health Insurance Database, the validity of ascertaining cirrhosis events in claims databases has been found to be satisfactory (32–34). In addition, newly diagnosed cirrhosis cases were classified using criteria involving at least 1 hospital admission code and 2 or more outpatient visits to enhance sensitivity and accuracy in ascertainment.

Several limitations should be acknowledged. Variations in body fat distribution exist among racial and ethnic groups, with Asians often having a higher tendency for central fat deposition and visceral adiposity, compared with Whites, even at the same BMI level (35). In addition, drinking culture and alcohol metabolism differed between Asian and Western populations (36,37), necessitating further studies in Western populations to validate our findings. Alcohol consumption was assessed only at baseline. While drinking habits may change over time and influence the classification of SLD subtypes, stability in these habits was observed (38). While acknowledging that abdominal ultrasound is less sensitive for detecting steatosis, it remains a practical and noninvasive tool for satisfactory diagnosis, particularly in the general population. A noteworthy point is that a substantial proportion of non-SLD individuals with cardiometabolic risk factors might have undetected steatosis through ultrasound. Conversely, the classification of cryptogenic SLD suggests a possibility of false positives by ultrasound. Despite these considerations, the practicality and feasibility of abdominal ultrasound make it a valuable diagnostic tool. Moreover, the acknowledgment that this study involves a single time-point assessment of hepatic steatosis is noted. In future investigations, the integration of multiple assessments to capture dynamic changes in steatosis over time will be crucial for gaining a comprehensive understanding of its role in the progression of advanced liver diseases. It is important to recognize the potential bias introduced by misclassification, particularly regarding individuals without SLD at baseline who may have developed it during the follow-up period. This misclassification could skew results toward finding no significant differences, despite the strength of the extended follow-up duration.

In conclusion, our study highlights distinct risks of cirrhosis and HCC associated with different SLD subtypes. Each subtype carries an elevated risk of cirrhosis and HCC when compared with non-SLD individuals. Notably, increased alcohol consumption among patients with SLD, specifically those categorized as MetALD or ALD, amplifies the risk of these end-stage liver diseases. Therefore, behavior modifications will play a crucial role in the clinical management of these conditions in the coming decades.

## CONFLICTS OF INTEREST

**Guarantor of the article:** Mei-Hsuan Lee, PhD.

**Specific author contributions:** M.-H.L.: study concept and design. M.-H.L.: acquisition of data. Y.-T.C. and M.-H.L.: analysis and interpretation of data. Y.-T.C. and M.-H.L.: drafting of the manuscript. Y.-T.C., T.-I.C., T.-H.Y., S.-C.Y., S.-N.L., X.-R.L., Y.-Z.G., C.-J.L., C.-W.H., J.-F.H., M.-L.Y., C.-F.H., C.-Y.D., W.-L.C., H.-I.Y., M.-L.Y., and M.-H.L.: critical revision of the manuscript for important intellectual content. M.-H.L.: acquisition of funding and study supervision.

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use. Other researchers may request the materials used through collaboration.

## Study Highlights

### WHAT IS KNOWN

- ✓ New nomenclature, transition from non-alcoholic fatty liver disease (NAFLD) to metabolic dysfunction-associated fatty liver disease (MAFLD) and ultimately to MASLD, aims to precisely categorize individuals with steatotic liver disease (SLD) and reduce stigmatization.
- ✓ Limited investigations exist on the proportions of individuals with various SLD subtypes and their associated risk for cirrhosis and hepatocellular carcinoma (HCC), necessitating future natural history and cost-effective studies.

### WHAT IS NEW HERE

- ✓ In a prospective study involving 332,175 adults with a median follow-up of 16 years, participants were categorized into subtypes, including MASLD, cryptogenic SLD, MASLD with excessive alcohol consumption (MetALD), and alcohol-related liver disease (ALD), based on ultrasonography findings, alcohol consumption patterns, and cardiometabolic risk factors.
- ✓ Multivariate-adjusted hazard ratios for HCC were 1.92 (95% confidence interval [CI] 1.51–2.44), 2.91 (95% CI 2.11–4.03), and 2.59 (95% CI 1.93–3.48) for MASLD, MetALD, and ALD, respectively, compared with non-SLD without cardiometabolic risk factors, with similar cirrhosis patterns.
- ✓ The large-scale study emphasizes divergent risks of cirrhosis and HCC associated with different SLD subtypes.
- ✓ The heightened risk of increased alcohol consumption among specific subtypes underscores the importance of behavioral modifications in clinical disease management.

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